PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Yoshiyuki MATSUMOTO , et al.

Appln. No.: 09/743,483

Confirmation No.: 2611

Filed: January 10, 2001

Docket No: Q62437

Group Art Unit: 1625

Examiner: HUANG, EVELYN MEI

For: THIOBENZIMIDAZOLE DERIVATIVES

SUBMISSION OF EXECUTED DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith is an executed Declaration Under 37 C.F.R. §1.132 signed by Naoki Hase to be considered with the Amendment filed on May 14, 2003.

Respectfully submitted,

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WASHINGTON OFFICE

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PATENT TRADEMARK OFFICE

Date: June 23, 2003

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DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexand
ria, VA 22313-1450

Sir:

I, Naoki Hase (name of declarant), hereby declare and state:

THAT I am a citizen of Japan;

THAT I have received the degree of master (degree) in 1993 (year) from Okayama University (name of institution);

THAT I have been employed by Teijin Limited (name of employer) since 1993 (date of employment), where I hold a position as research scientist (job title), with responsibility for pharmacological evaluation (job responsibilities);

THAT I am a co-inventor of the subject matter disclosed and claimed in the above-identified application.

THAT the following *in vivo* pharmacological test was carried out by me or under my supervision.

The *in vivo* test results below demonstrate the pharmacological effects of compounds of the present invention in diseases involving chymase by migrating into the blood and tissues and inhibiting chymase as a result of oral administration.

Pharmacological Evaluation of Increased Dermal Vascular Permeability in Guinea Pigs by Intracutaneous Administration of Human Chymase

Test Animals: Male Hartley guinea pigs (age 7 weeks at purchase, age 9-11 weeks at the time of the study).

Test Methods: 0.5% CMC-Na solutions of the test compounds were administered orally (30 mg/kg, 100 mg/kg). After 1.5 hours, the backs of the guinea pigs were shaved under ether anesthesia, and pigment (Evans Blue, 1% in saline, 4 ml/kg, i.v.) was administered intravenously. Human recombinant chymase (1.67, 0.5 μg/site), vehicle and saline were administered at intervals by intracutaneous administration into the skin of the backs of the animals (50 μl/site). The animals were sacrificed by exsanguination 20 minutes later, followed by collecting samples of the skin using the presence of a bluing spot on the skin of the back as an indicator. The amount of pigment present was then measured with a spectrophotometer. 0.15 M NaCl, 0.1 mg/ml BSA and 10 mM Pi-Na (pH 7.6) were used as vehicles for the chymase. When the animals were sacrificed by exsanguination, serum and a portion of the skin at which chymase

was not administered were sampled, and those samples were then measured for concentration of the test compounds. Data from these tests is shown in the following Table.

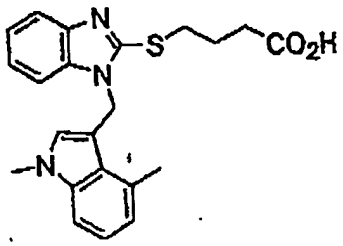
Results: An increase in dermal vascular permeability was observed correlating with the dose of chymase following intracutaneous administration of chymase. Simultaneously, the group of compounds of the present invention were confirmed to be present in both serum and skin.

Compound No.	Dose p.o. (mg/kg)	Vasc. Leak. by h-chymase (%inhibition)*	Conc. of compound (110 min)		
			Serum (nmol/ml)	Skin (nmol/g)	Kp (Skin/Serum)
459	30	44.2	164.4±51.8	47.3±15.3	0.29±0.02
	100	63.6	374.1±62.6	118.8±28.6	0.33±0.05
455	30	35.2	n.t.	n.t.	-
	100	54.1	n.t.	n.t.	-
Compound A	30	54.5	103.5±26.4	28.4±9.1	0.27±0.03
	100	84.8	179.2±35.6	73.4±8.8	0.43±0.13
Compound B	30	48.3	n.t.	n.t.	-
	100	77.0	n.t.	n.t.	-

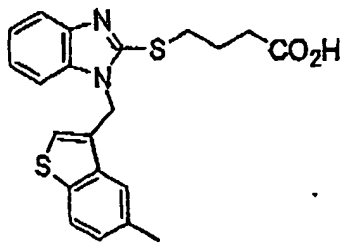
*: inhibition of vascular leakage (by 1.67 μg of human chymase)

**: n.t.: not tested; n.d: not detected.

Compound A: 4-(1-((1,4-Dimethylindole-3-yl)methyl)benzimidazole-2-ylthio)butyric acid



Compound B: 4-(1-((5-Methylbenzo[b]thiophene-3-yl)methyl)benzimidazole-2-ylthio)butyric acid



I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: June, 6, 2003

Research Scientist
Naoki Hase
Name and Title of Declarant